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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,430	10/12/2000	Christopher E. Walsh	35052/204373 (5052-53)	7095
§26	7590	01/14/2004		
ALSTON & BIRD LLP BANK OF AMERICA PLAZA 101 SOUTH TRYON STREET, SUITE 4000 CHARLOTTE, NC 28280-4000			EXAMINER QIAN, JANICE LI	
			ART UNIT 1632	PAPER NUMBER

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/689,430

Applicant(s)

WALSH ET AL.

Examiner

Q. Janice Li

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 December 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8-12, 14-20, 58-77, 79-88 and 90-92 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-12, 14-20, 58-77, 79-88, and 90-92 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 June 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) ☐ Other: _____

DETAILED ACTION

The amendment and response filed on December 15, 2003 has been entered. Claims 7 and 13 have been canceled. Claims 15 and 91 have been amended. In view of the arguments presented in the response, the prosecution is hereby REOPENED. Claims 1-6, 8-12, 14-20, 58-77, 79-88, and 90-92 are pending and under current examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-6, 8-12, 14-18, 20, 58-77, 79-88, and 90-92 stand rejected and the rejection has been modified under 35 U.S.C. 103(a) as unpatentable over *Gnatenko et al* (1996, IDS/85), *Dwarki et al* (US 6,221,646), *Dwarki et al* (1995, IDS/15), in view of *Carter et al* (US 5,866,696), *ILL et al* (US 5,744,326), and evidenced by *Vorachek et al* (J Bio Chem 2000 Sep;29031-41).

Gnatenko et al teach a recombinant adeno-associated virus vector comprising a B-domain deleted factor VIII (given as about nucleotides 419-4835 of SEQ ID No: 1) operably linked to a core vWF promoter and an SV40 polyadenylation signal. They teach the vector is useful for hemophilia A gene therapy. *Gnatenko et al* do not teach using AAV ITR as the only promoter.

Dwarki et al teach a rAAV selected from anyone of the AAV serotype 1-7 and comprising an AAV ITR (column 5, lines 3-4), wherein the vector could encode a factor VIII (column 9, line 44) operably linked to an AFP enhancer and albumin promoter (column 6, line 35), which is a liver-preferred expression control element and has a HNF1 binding site as evidenced by *Vorachek et al*; the vector further comprising polyadenylation sequence (column 10, line 11). *Dwarki et al* also teach a method of producing rAAV stock and at 120 hrs, the total viral particles reached about 10^{12} . (9×10^{11} , table 1). Although *Dwarki et al* do not particularly teach that factor VIII is B domain deleted factor VIII in the cited patent, they do teach the size limitation for AAV vectors (column 7, lines 43-55), and in an 1995 publication, *Dwarki et al* actually use the B domain deleted FVIII for *in vivo* gene therapy with a retroviral viral expression vector. *Dwarki et al* teach that an AAV vector carrying a heterologous gene of interest was positioned between two AAV ITRs, which serve as recognition signals for DNA replication and packaging, *Dwarki et al* do not teach that ITR can be used as the sole promoter for expressing the heterologous gene of interest.

Carter et al teach that contrary to the conventional wisdom, they discovered that AAV ITR itself is sufficient as a transcription promoter, and if a AAV vector carrying a therapeutic gene such as CFTR is placed immediately adjacent to the AAV ITR, it can be functionally expressed in human cells to correct the related physiological defect such as cystic fibrosis. *Carter et al* also teach that it is desirable to use the AAV ITR rather than the usual AAV p5 or other promoter because the size limitation of AAV vector

Art Unit: 1632

(column 2, lines 19-49), "IT IS IMPORTANT TO DEVELOP THE SMALLEST POSSIBLE REGULATORY SEQUENCES, SUCH AS TRANSCRIPTION PROMOTERS AND POLY A SIGNAL".

ILL et al teach that certain viral cis-acting post-transcriptional regulatory element could enhance expression of intronless genes by facilitating the export of the gene transcript from the nucleus into the cytoplasm of the cell (abstract). In a preferred embodiment, they disclose a liver-specific enhancer (SEQ ID No: 1) having an enhancer derived from hepatitis B virus (Enh1) given about (95.3% sequence homology with) 150-278 of instant SEQ ID No: 1 operably linked with a B-domain deleted FVIII and expressing such *in vivo* in a pharmaceutical composition at therapeutic levels (Fig. 6).

Obviously, it is well known in the art that AAV is a desirable expression vector for purpose of delivering a heterologous gene of interest to a patient, it is also well known in the art that the size limitation of the AAV vector could be resolved by truncating the non-essential region of the gene of interest, and by developing the smallest possible regulatory elements, such as using the AAV ITR as the transcription promoter. It is additionally well known in the art that liver-specific enhancer such as Enh1 could be used in combination with B-domain deleted FVIII to promote the secretion of the transgene product.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by *Gnatenko et al*, to include the elements as taught by *Dwarki et al*, *Carter et al*, *ILL et al*, so that the expression vector would be more efficient for hemophilia A gene therapy with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to

Art Unit: 1632

modify the claimed vector because given the numerous teachings in the art regarding various elements making the vector more efficient and suitable for gene therapy, it falls within the bounds of the optimization for the ordinary skilled to make an efficient expression vector. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 2 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Gnatenko et al* (1996, IDS/85), *Dwarki et al* (US 6,221,349), *Dwarki et al* (1995, IDS/15), *Carter et al* (US 5,866,696), and *ILL et al* (US 5,744,326) as applied to claims 1, 3-6, 8-12, 14-18, 20, 58-77, 79-88, and 90-92 above, and further in view of *Gao et al* (US 6,258,595).

Claims 2 and 19 are further directed to a DNA spacer in the rAAV construct, the combined teachings of *Gnatenko et al*, *Dwarki et al*, *Carter et al*, and *ILL et al* fail to teach such a spacer. However, before the instant application was filed, *Gao et al* teach to include a DNA spacer in the construct of recombinant AAV vector as an optional element in the design of the AAV vector (the paragraph bridging columns 12 and 13).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by of *Gnatenko et al*, *Dwarki et al*, *Carter et al*, and *ILL et al* by simply including a DNA spacer in the vector construct as taught by *Gao et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention to optimize and

improve the expression capacity of the rAAV vector. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

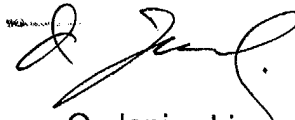
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 571-272-0734. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.


Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (571) 272-0532.


Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JANICE LI
PATENT EXAMINER



Q. Janice Li
Patent Examiner
Art Unit 1632


January 12, 2004


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